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Original Research

Angiogenic factors and evaluation of vascular status in preeclampsia

Preeclampsia vascular evaluation

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Abstract
Aim: The aim of this study was to measure serum levels of the angiogenic factors nitric oxide (NO), soluble endoglin (s Eng), soluble fms-like tyrosine kinase-1 (s Flt-1), placental-derived growth factor (PIGF) and vascular endothelial growth factor (VEGF) and to measure uterine and umbilical arterial blood flow using Doppler ultrasonography to investigate the physiopathology of preeclampsia and endovascular dysfunction by comparing brachial artery dilatation and the thickness of the carotid artery with normal pregnant women.
Material and Methods: Forty pregnant women with preeclampsia and 40 healthy pregnant women (control group) were recruited for the study in April 2011 and October 2011 at Van Yuzuncu Yil University. Systolic and diastolic blood pressure, urinary protein in spot urine samples, complete blood counts, aspartate transaminase (AST), alanine aminotransferase (ALT) levels of sEng, sFlt-1, VEGF, PIGF and NO, and APGAR scores at one and five minutes after birth were recorded and compared in all patients. Intima-media thickness of the carotid artery, brachial artery dilatation and umbilical artery Doppler parameters of all pregnant women were assessed and recorded.
Results: When compared to the control group, systolic and diastolic blood pressures urinary protein in spot and 24-hour urine collection, levels of AST, ALT and sFlt-1, and uterine artery Doppler parameters were significantly higher, whereas VEGF, platelet count and APGAR scores at one and five minutes after birth were lower in the preeclampsia group ($p<0.001$). Brachial artery dilatation before obstruction was found to be insignificant in both groups, while post-obstructive dilatation was found to be significantly higher in the control group.
Discussion: Uterine artery Doppler evaluation, assessment of brachial artery dilatation and measurement of VEGF and sFlt-1 levels seem to be useful in pre-eclampsia.

Keywords
Angiogenic; Preeclampsia; Vascular; Brachial Artery; Nitric Oxide

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Introduction

Despite significant developments in obstetric diagnosis and treatment services, preeclampsia is one of the leading causes of maternal and fetal morbidity and mortality in developed countries [1]. Diagnosing preeclampsia before the clinical picture emerges will undoubtedly provide an important advantage for the physician. In case of early diagnosis, there will be options to protect the patient from this entity or delay the onset of the clinical picture, and this will have positive effects in terms of maternal and neonatal results [2].

The pathophysiological development of preeclampsia is multifaceted, and it is known that it develops as a result of insufficient invasion of maternal spiral arteries by endovascular cytotrophoblasts. Following this event, spiral arteries cannot sufficiently convert from low-capacity high-resistance vessels to high-capacity low-resistance uteroplacental vessels. Since the migration of endovascular trophoblasts occurs in the early period of pregnancy, it can be stated that preeclampsia starts long before the clinical picture emerges.

Impairment in the uterine artery Doppler is among the indications of this [3]. In addition, impairment in brachial artery dilatation in preeclampsia, where endothelial damage plays a part, may be associated with NO secretion and endothelial damage [4].

VEGF, PlGF, sFlt-1, sEng, NO and what their receptors produce have been revealed, and the role of angiogenic factors in the pathophysiology of the disease has been emphasized. These factors can initiate the activation of endothelial cells, which is a well-defined event in preeclampsia. Among these factors, the balance between VEGF and sFlt-1, which is its natural antagonist, and the changes they show in preeclamptic pregnant women, have attracted the attention of many researchers; it has been emphasized that they can be useful in revealing the etiopathogenesis of preeclampsia, which is a public health problem [5].

We also aimed to reveal the relationship that may be important in terms of preeclampsia pathophysiology by examining these parameters in our preeclamptic patient group, normal pregnant group and postpartum group.

Material and Methods

This study was conducted between April 2011 and October 2011 at Van Yuzuncu Yil University. The study has been approved by the Van Yuzuncu Yıl Üniversity Ethics Committee. The female participants, who were included in the study, were informed about the study and their verbal and written consents were obtained. Between January and April 2011, 40 patients were included in the study group according to their last menstrual period or if they did not remember their last menstrual periods, it was examined whether they were diagnosed with preeclampsia according to ultrasonographic fetal biometric measurements and ACOG 2015 Preeclampsia criteria. Similarly, 40 healthy pregnant women of the same age and in the same week who applied for pregnancy control were included in the study. The pregnant women included in the study group postpartum were invited and reevaluated at 6 weeks postpartum. Preeclampsia diagnosis was established in the presence of 140/90 mmHg and higher blood pressure (in two measurements performed every other six hours) and proteinuria (at least 300 mg or higher in 24-hour urine) developing after the 20th week of pregnancy in the pregnant woman who had been previously normotensive. In the healthy pregnant group included in the study, it was ensured that the age and gestational week were similar to the patient group. Exclusion criteria were as follows: maternal diabetes, renal disease, multiple pregnancy, fetal anomaly, cardiovascular disease, IUEF (Intrauterine ex fetus).

Information of the patients in the study and control groups were recorded in research forms, which had been prepared previously. These forms included patients' age, gravida, parity, pregnancy week, systolic-diastolic blood pressure, protein in spot urine, hemoglobin (Hgb), platelet count, urea, creatinine, liver function tests, Aspartate aminotransferase, Alanine aminotransferase, NO, s Eng, sFlt-1, PlGF, VEGF values in pregnancy and postpartum period, carotid artery intima thickness, brachial artery width and dilatation value, uterine artery RI-PI-S/D value, uterine artery notch, umbilical artery RI-PI-S/D values, 1st- and 5th-minute APGAR score of the infant.

Ultrasonographic evaluations of the preeclamptic (n=40) and healthy pregnant (n=40) groups were conducted during pregnancy and postpartum period using a General Electric Medical Systems Voluson 730 Expert 3-dimensional color Doppler device. The Carotid artery intima thickness was measured using transabdominal 2.5-7.5 mHz convex probe. Uterine artery doppler was performed to measure RI-PI-S/D, uterine artery notch and umbilical artery RI-PI-S/D values. Arterial and venous flow was stopped for 5 minutes after the arm was inflated with a blood pressure cuff to measure the dilatation due to brachial artery flow. Then, the brachial artery dilatation was measured after the flow returned to normal. The blood samples taken from antecubital veins of the patients were centrifuged at 4000 rpm/10 min (Nüve NF 800R, Ankara, Turkey), placed in Eppendorf tubes, and kept at –80 °C in an unlighted environment. In serum samples prepared after the collection of the samples of all groups, the NO, sEng, sFlt-1, PlGF, VEGF levels were examined through the quantitative sandwich enzyme immunoassay. The measurements were performed in the Farmasina medical laboratory.

Statistical analysis

After the patient data were transferred to the SPSS 16.0 for Windows package program in a computer environment, statistical analysis was carried out. While descriptive statistics for continuous variables were expressed as mean, standard deviation, minimum and maximum values, the categorical variables were stated as number and percentage. Student's t-test was used to compare the mean scores of the groups in terms of continuous variables. In order to determine the relationship among these variables, Pearson's correlation coefficients were calculated. In addition, the Chi-square test was performed to determine the relationship between the groups and categorical variables. In the calculations, the level of statistical significance was determined as <0.05 - <0.01

Results

A total of 80 pregnant women diagnosed with preeclampsia in the third trimester (n=40) and at a similar age (n=40) were included in the study population. The cases were invited and

reevaluated in the 6th week postpartum. Values were given as mean ± standard deviation. Clinical and biochemical values of preeclampsia and normal pregnant patient groups are given in Table 1. There was no statistical difference between age, parity and gravida in both groups (p>0.05). The difference in platelet, AST, ALT, 1. minute APGAR, 5. minute APGAR values between the preeclampsia group and the normal pregnant group was statistically significant (p< 0.001).

The mean serum level of NO in the preeclamptic pregnant group was detected as 19.60±10.08, while it was 18.53±12.39 in the healthy pregnant group, and the difference was not found to be statistically significant (p=0.376). The mean serum level of sENG in the preeclamptic pregnant group was detected as 8.74±2.51 ng/ml, while it was 8.77±2.07 ng/ml in the healthy pregnant group, and the difference was not found to be statistically significant

(p=0.504). The mean serum level of sFlt-1 in the preeclamptic pregnant group was detected as 12.9±10.5 pg/ml, while it was 8.34±10.2 pg/ml in the healthy pregnant group, and the difference was found as statistically significant (p < 0.001). The mean serum level of PlGF in the preeclamptic pregnant group was detected as 303.71±21.83, while it was detected as 349±212.56 in the healthy pregnant group, and the difference was not found to be statistically significant (p=0.498). The mean serum level of VEGF in the preeclamptic pregnant group was detected as 156.3±11.20 pg/ml, it was determined as 212.40±12.65 pg/ml in the healthy group, and the difference was found to be statistically significant (p < 0.001) (Table 2).

Serum NO, sEng, sFlt-1, PlGF, values of preeclamptic and healthy pregnant groups in the postpartum period were compared, and no statistical difference was found (p>0.05).

The mean serum level of NO in the preeclamptic pregnant group was detected as 9.22 ±2.19, while it was 8.64 ±4.04 in the healthy pregnant group, and the difference was not found to be statistically significant (p= 0.320). The mean serum level of sENG in the preeclamptic pregnant group was detected as 5.99±3.34 ng/ml, while it was 5.42±2.13 ng/ml in the healthy pregnant group, and the difference was not found to be statistically significant (p=0.634).

The mean serum level of sFlt-1 in the preeclamptic pregnant group was detected as 5.6 ±1.69 pg/ml, while it was 5.65 ±3.68 pg/ml in the healthy pregnant group and the difference was found as statistically significant (p= 0.840). The mean serum level of PlGF in the preeclamptic pregnant group was detected as 300.39 ±30.03, while it was detected as 311.30 ±124.65 in the healthy pregnant group, and the difference was not found to be statistically significant (p=0.283). The mean serum level of VEGF in the preeclamptic pregnant group was detected as 212.40±122 pg/ml, it was determined as 291.16±166 pg/ml in the healthy group, and the difference was found to be statistically significant (p=0.014).

While the carotid artery intima thickness of preeclamptic pregnant women was determined as 0.53±0.04 mm, this value was 0.54±0.04 mm in the healthy pregnant women, and the difference among them was not statistically significant (p=0.807). While the preobstruction brachial artery width of the preeclamptic pregnant women was found as 3.76±0.46 mm, it was determined as 3.75±0.44 mm in the healthy pregnant women, and the difference among them was not statistically significant (p=0.957). While the postobstruction brachial artery width of the preeclamptic pregnant women was determined as 3.97±0.63 mm, it was determined as 4.60±0.56 in the healthy pregnant women and the difference was found as statistically significant (p < 0.001). Comparison of the uterine artery doppler of the preeclamptic pregnant women and healthy pregnant women was found to be statistically significant (p < 0.001). While the rate of notch in the uterine artery was 66% in the preeclamptic pregnant women, it was 6% in healthy pregnant women (Table 3).

Table 1. Clinical and biochemical values of the patient groups

	Preeclamptic Pregnant Group	Healthy Pregnant Group (n = 40)	p
Age (years)	34,60± 8.00	33,25± 8,23	0.471
Gravida	5,18 ±2.55	4.85±2.52	0.528
Parity	4.05±1.92	3.75±2.05	0.494
Pregnancy Week	33.60±3.64	33.60±3.64	1.00
Systolic blood pressure (Mm Hg)	153.25 ± 11.85	114±9.04	<0.001
Diastolic blood pressure (Mm Hg)	97.00 ± 8.83	73.00±9.11	<0.001
Protein in spot urine amount (mg / dl)	314 ±13	10±2	<0.001
Hgb (g/dl)	12.53 ±1.45	12.69±1.63	1.00
Platelet (10^3/uL)	196 .88±94.95	262.73±54.38	<0.001
AST (U/L)	41.08 ±51.86	22.20±9.87	<0.001
ALT (U/L)	40.83± +62.74	18.73 ±11.10	<0.001
1. minute APGAR	5.55±1,45	6.90±0.96	<0.001
5. minutes APGAR	7.55±1.84	9.30±0.91	<0.001

Table 2. Angiogenic factor levels in preeclamptic and healthy pregnant women during pregnancy

	Preeclamptic Pregnant Group	Healthy Pregnant Group (n = 40)	p
NO (µM)	19.60±10.08	18 .53±12.39	0.376
sEng (ng/ml)	8.47±2.51	8.77±2.07	0.504
sFlt.1 (ng/ml)	12.90±10.56	8.34 ±10.2.	0.001
PlGF (pg/ml)	303.71±21.83	349.92±212.56	0.498
VEGF (pg/ml)	156.3 ±11.20	212.40 ±112.65	0.001

Table 3. Doppler ultrasonography comparison of preeclamptic and healthy pregnant women

	Preeclamptic Pregnant Group	Healthy Pregnant Group (n = 40)	p
Carotid artery intima thickness (mm)	0.53±0.04	0.54±0.04	0.807
Brachial artery width before (mm)	3.76±0.46	3.75±0.44	0.957
Brachial artery width after (mm)	3.97±0.63	4.60±0.56	0.001
Uterine artery doppler			
RI	0.77±0.18	0.54±0.08	0.001
PI	1.29±0.66	0.63±0.33	0.001
S/D	4.04±1.16	2.67±0.52	0.001
Notch	%66	%6	0.001
Umbilical artery			
RI	0.58±0.12	0.56±0.09	0.873
PI	0.65±0.35	0.75±0.24	0.523
S/D	2.66±0.59	2.68±0.47	0.793

Discussion

Despite developments in the field of obstetrics, preeclampsia is still the second most common cause of maternal and fetal morbidity and mortality after embolism. The classic diagnosis triad is hypertension, proteinuria and edema observed following the 20th week of pregnancy [6]. Our study tries to understand the relationship between vascular structures and endovascular dysfunction in preeclampsia based on soluble endoglin (sEng), soluble fms-like tyrosine kinase 1 (sFlt-1), vascular endothelial growth factor (VEGF), PIGF and NO measurements and doppler USG analysis. Defining the circulating two anti-angiogenic proteins (s Eng and s Flt-1) will help us understand the connection between abnormal placentation and endothelial dysfunction. The increase in the production of these two anti-angiogenic proteins is stated to induce endothelial dysfunction by inhibiting PlGF, VEGF circulating proangiogenic factors [7].

In our study, the mean sEng level was determined as 8:47±2:51 ng/ml in the preeclamptic pregnant group, while in the healthy pregnant group, it was detected as 8.77±2:07 ng/ml, and the difference between them was not statistically significant (p>0.05). Levine et al. in their study, in which they investigated sEng level, examined a total of 552 pregnant women with 72 preterm preeclampsia (<37 weeks), 120 term preeclampsia (≥37 weeks), 120 gestational hypertension, 120 normotensive SGA and 120 non-normotensive SGA. In this study, it was revealed that the circulating sEng level increased significantly 2-3 months before the onset of preeclampsia [8]. Lubis et al. in the study, in which they predicted early-onset preeclampsia, uterine artery circulation and PlGF levels were effective in predicting preeclampsia, and no change in s Eng levels was observed [9].

In our study, it was determined that the mean sFlt-1 level of the preeclamptic pregnant group was 12.90±10.5, while it was 8.34±10.2 in the healthy pregnant group, and the difference between them was statistically significant (p < 0.001). The receptor sFlt-1 associated with maternal endothelial dysfunction is a component of preeclampsia pathogenesis [10]. Levine et al. put forward the increased expression of sFlt-1 and decreased expression of VEGF. More importantly, it was revealed that the administration of exogenous sFlt-1 on rats caused preeclampsia-like disease alone [11].

In our study, the serum level of VEGF of the preeclamptic pregnant group was determined as 156.3±112.0, while it was detected as 212.40±112.65 in the healthy pregnant group, and the difference was found to be statistically significant (p<0.001). VEGF is known to stimulate vasodilation and angiogenesis. Although this isoform is up-regulated in preeclampsia, its metabolic activities can be blocked by other proteins that bind to VEGF and inhibit its functions. Both sFlt-1 and sEng bind to VEGF and inhibit its functions [12]. In the study conducted by Tang, the increased expression of sFlt-1 and decreased expression of VEGF in preeclampsia were revealed [13]. Circulating free PlGF levels decrease in preeclampsia [14]. Binding to circulating sFlt-1, which is found at higher levels, was shown as the reason for this. In our study, when the mean serum level of PlGF in the preeclamptic pregnant group was compared with the normal pregnant group, the difference was not found to be statistically significant (p>0.05).

In our study, when the serum level of NO in preeclampsia pregnant group was compared with the serum level of NO in the healthy pregnant group, the difference was not found to be statistically significant (p>0.05). Noorbakhsh M et al. determined that serum nitric oxide levels were significantly higher in preeclamptic women compared to the normotensive pregnant women, and found that there was a (+) correlation between nitric oxide levels [15]. Valeria C et al. determined that the levels of plasma NO metabolites decreased in preeclamptic patients [16]. In a study conducted by Silver et al., it was reported that there was no difference between preeclampsia and the pregnant group, which is consistent with our study [17]. The brachial artery dilatation test is accepted as an in vivo marker of vascular "function", and IMK measurement of carotid arteries is a "structural" marker of the vascular damage degree [18]. In our study, no significant difference was found when the carotid artery intima–media thickness and umbilical artery dopplers were compared in preeclampsia pregnant group and normal pregnant group. In our study, the mean value of carotid artery intima–media thickness of our patient population was below the pathological lower limit of 0.53 mm. Akhter et al. stated that there is a relationship between carotid artery intima thickness and pre-eclampsia t and cardiovascular diseases, and this non-invasive method should be used [19]. In a study by Blaauw et al., they excluded all risk factors of 22 nulliparous preeclampsia and 22 normal pregnant women, and it was observed that carotid artery intima media thickness increased in nulliparous preeclampsia patients [20]. After 4 years, Blaauw et al, who examined the same preeclampsia and normal pregnant patient group, did not increase carotid artery intima thickness in preeclampsia cases and reported that this may be a temporary adaptive condition in preeclampsia [21].

In our study, it was found that the expected dilatation was not observed after the test in the preeclampsia pregnant group in the brachial artery dilatation test, performed on the preeclampsia pregnant group; however, the posttest brachial artery dilatation was at a sufficient level in the normal pregnant group. Dilatation due to the increased flow in peripheral arteries was shown to be largely provided by NO secreted from the endothelium. Dilatation due to reactive response occurring after ischemia is known to be an endothelium-dependent phenomenon. This a repeatable and non-invasive method, which patients can easily tolerate and is applied to determine endothelial function, is widely used in clinical studies. A dilatation of 10 percent is generally accepted as the lower limit value [22]. In our study, the brachial artery width, which was 3.7 mm in the preeclampsia pregnant group before the test, was found as 3.9 mm after the test, and the dilatation difference, which was 2 mm in average, was observed below the dilatation limit of 10% in line with the literature. In a study conducted by Filho et al., it was reported that brachial artery dilatation test values were lower in the preeclampsia pregnant group compared to normal pregnant women, and doppler values were higher in uterine artery compared to the control group, while there was no difference in carotid artery intima-media thickness [23]. Malhotra AS et al, suggested that FMD be used as a noninvasive marker to predict preeclampsia development [24]. On the other hand, Praciano De Sousa et al. reported that the brachial artery FMD as independent parameters did not

have a good predictive value for hypertensive disorders in the second trimester [25].

Conclusion

We think that uterine artery Doppler, assessment of brachial artery dilation and measuring VEGF, sFlt - 1 levels are helpful in predicting preeclampsia. It can be concluded that brachial artery dilation test can be effective in predicting hypertension in patients in parallel with the endovascular dysfunction developing as a result of NO dysfunction.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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